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MULTIPLE SCLEROSIS AND BIO-PHYSICO-METRIC APPROACH: EFFECTS OF FOCUSED MECHANO-ACOUSTIC VIBRATIONS

G. Barassi[1], L. Prosperi[1], M. Panunzio[2], A. Frattaruolo[3], C. Marinucci[1], C.E. Gallenga[4], A. Moccia[1], G.L. Matera[1], L. Zeppa[5] and P.E. Gallenga[1]

[1] Center for Physiotherapy, Rehabilitation and Re-Education (Ce.Fi.R.R.), venue "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy;
[2] Responsible Research Hospital, Campobasso, Italy;
[3] San Stef.Ar. Molise Center, Campobasso, Italy;
[4] Section of Ophthalmology, Department of Biomedical Sciences and Specialist Surgery, University of Ferrara, Ferrara, Italy;
[5] Complex Operating Unit of Ophthalmology, San Giuseppe Moscati National Hospital Trust, Avellino, Italy.

**Correspondence to*:
Giovanni Barassi,
Center for Physiotherapy, Rehabilitation and Re-Education (Ce.Fi.R.R.),
Venue "G. d'Annunzio" University of Chieti-Pescara,
66013 Chieti, Italy.
e-mail: coordftgb@unich.it

ABSTRACT

Multiple sclerosis (MS) is a complex disease involving the nervous system with severe musculoskeletal manifestations in terms of postural-biomechanic functionality and stability, paired with a worsening of the visual system. Among the most interesting therapies for neuromuscular stimulation of the human body is vibration therapy, in particular in the form of Focused Mechano-Acoustic Vibrations (FMAVs), whose therapeutic efficacy, however, is still not fully understood in the field of neurodegenerative diseases such as MS. Therefore, in this observational pilot study we evaluated the evolution of clinical parameters such as fatigue, measured by the Fatigue Severity Scale (FSS), and postural stability, measured by a Stabilometric Analysis (SA), in a sample of 12 MS patients who underwent 3 weekly sessions for 4 weeks of FMAVs. At the end of the study, we observed a significant improvement in the FSS value in response to FMAVs treatment, although the results in terms of SA were mixed. In conclusion, FMAVs appear to be a promising and safe treatment for MS patients, but further and more in-depth studies on the topic are needed to clarify their role in the field of rehabilitation.

KEYWORDS: *Vibrations, neurodegenerative disease, multiple sclerosis, muscle spasticity, physical therapy modalities, rehabilitation, gait analysis, fatigue*

INTRODUCTION

Different experiences over the years have shown that when a mechanical vibration (100-200 Hz) is applied to a relaxed muscle, it causes a tonic contraction of the vibrating muscle which can be recorded by EMG and the resulting tonic vibration reflex (TVR) is framed as an autogenous reflex and this obviously strongly affects the spinal reflexes (1). Most of these effects have been found to arise from vibration-induced activation of spindle Ia afferents (presynaptic inhibition) demonstrated by the presynaptic inhibition of the T reflex and the H reflex (2-4).

These considerations are relevant for people affected by Multiple Sclerosis (MS), who can manifest various combinations of disabilities, such as physical dysfunction (motor weakness, spasticity, sensory dysfunction, vision loss,

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ataxia, etc.), fatigue, pain, incontinence, and cognitive deficits (memory, attention, executive dysfunction). MS has various presentation patterns (5), which include:

- "Relapsing-remitting" MS (80% of all MS cases), presenting with exacerbations and remissions, potentially evolving into a "secondary-progressive" form of MS with progressive disability that occurs between acute “attacks” of the disease;
- "Primary-progressive" MS (15% of all MS cases), in which progressive disability can manifest itself from the onset onwards;
- "Progressive-relapsing" MS (5% of all MS cases), in which the disease gradually worsens and then manifests itself with discretely severe “attacks”.

MS can be accompanied by psychosocial, behavioral, and working capacity alterations. These have a multidimensional impact on the activity (function) and participation of a person in the activities of daily, social and working life, with a significant impact from a social cost point of view (6).

A consultation of MS rehabilitation studies on balance, weakness, cardiovascular fitness, ataxia, fatigue, bladder dysfunction, spasticity, pain, cognitive impairment, depression and pseudobulbar affections concluded that fatigue affects approximately two thirds of people with MS (7).

MS-related fatigue is a complex and subjective symptom characterized by a lack of energy or an overwhelming sense of physical and / or mental fatigue. Fatigue is associated with a poorer quality of life (even when controlling the severity of the disease) and is one of the main reasons for retirement from work in MS patients (8).

Fatigue management has been identified as a priority for the quality of life of MS patients. In routine clinical care, drug treatments tend to be the first choice, with behavioral interventions and exercises considered as alternative or additional treatment options (9). In many cases, patients are never offered these non-pharmacological treatment options, and this is concerning as current evidences suggest that drug interventions to date are largely ineffective, while exercise and behavioral interventions have greater effects (9). Evidence for the end-of-treatment effects of different types of exercise interventions suggests that there is no single optimal exercise modality to strengthen muscle function in MS, but rather the choice of the type of exercise may depend on the specific combination of symptoms of MS, by the level of disability of the patient and his/her needs and preferences (9).

The mechanisms by which exercise improves fatigue will therefore differ for different types of personalization of the rehabilitation treatment (10).

Also, the results of the various experiences for balance work are moderate, so this rehabilitation practice should be used with some caution and applied according to the differences in the nature of the interventions. Balance exercise interventions include hippotherapy, vestibular rehabilitation and eye movement and balance exercises (11-13). However, since in this category there are only end-of-treatment effects, it is uncertain if these effects will last over time.

Furthermore, it must be considered that postural and biomechanical adjustments can be largely influenced by vision, and this is even more true in MS patients.

Looking at the association between eye diseases and MS, it must be highlighted that in the typical MS optic neuritis the inflammatory recruitment from the vascular bed to the perivascular space, then to the parenchyma of the central nervous system, is the result of chemokine activity. In fact, a key role is played by the chemokine ligand CXCL-10 and its receptor CXCR3 (14) on a predisposing genetic substrate (altered mode of immune response), peculiarly in carriers of histocompatibility antigens HLA-A3, B7, DRW2. The distribution of genetic factors plays an important role in the topographical clustering of phenotypes.

In MS, the initial plaques of demyelination are generally not particularly extensive, and present only in the white matter of the brain or of the medulla and optic nerves, causing a so called retrobulbar optic neuritis (RON). In the advanced stages, plurifocal lesions are associated with pyramidal, cerebellar and sensory syndrome. RON takes on particular importance as it can constitute the first isolated, acute, generally unilateral and transient manifestation of MS, and precede in time - up to 10 to 20 years - other subsequent symptoms, with a probability of 34% in males and 74% % in females (15).

Spontaneous retrobulbar pain or pain caused by movements of the bulb would be related to contractions of the oculomotor muscles, which would cause stretching of the optic nerve inflamed meninges, inside the orbital cone or the fibrous/osteo-fibrous ring of Zinn (16) and to the fascial wrapping of the medial rectus and superior rectus (17). Moreover, temporal pallor with shading of the margin of the optic disc is a late sign of Wallerian-like degeneration. The functional deficit translates into centro-cecal scotoma, due to involvement of the papillo-macular bundle, with functional visual damage, reduction in amplitude and increase in latency of the VEPs, dyschromatopsia of the red-green axis, which is superimposed by the yellow-blue axis in the presence of papillary oedema (18). The conduction delay derives from the modification of ionic concentrations along the axons and from the slowing of the axonal flow with a reduction of the chemical mediators of the synapses and exhaustion of the response. This translates into difficulty in systemic motor control with fatigue gradually worsening as the systemic damage progresses.

Usually, in the initial stages, the scotoma regresses spontaneously, although a reduction in contrast sensitivity with a general sensation of visual blurring is often evident due to the involvement of the papillo-macular bundle; in subsequent phases it may then be associated with pars planitis, with general signs of motor difficulties and fatigue, attention and memory disorders, detectable with psychometric tests. Diplopia due to nuclear lesions of the III, IV, VI cranial nerve, and nystagmus complete the typical MS Charcot's symptomatic triad (18); also, venous engorgement with whitish sleeves, expression of periphlebitis with lymphoplasmacytic infiltration at two-three papillary diameter away from the optic disc, can appear, until leading the patient into the territory of low vision.

Low vision is an irreversible pathological condition characterized by reduced central visual acuity (typical of demyelinating pathologies), which is also essential for orientation and independent walking (19), inducing decisive consequences on postural behavior (20). The tonic-postural system consists of peripheral receptors (afferent and efferent nerve pathways) and peripheral and central nervous system. The impairment of the visual entrance causes an imbalance that spreads over the whole muscular chains, in an ascending or descending and also spiral manner. The imbalance, the bascules and the rotation are projected to the foot sole and can be recorded with specific 3D digitalized baropodometric platforms.

The evaluation with a visually central impaired patient, as for MS, shows a hypercharge on the side of the dominant eye (21), whilst in peripheral defects there is a contralateral overload compared to the dominant one (22).

Concerning the muscular stimulation aspects of rehabilitation, we know that if a vibratory stimulation is applied to a spastic muscle, it influences its tone (1); at the same time when the stimulation is applied to the antagonist muscle, it may cause a reciprocal inhibition of the spastic muscles: neurophysiologically, this phenomenon would be linked to presynaptic inhibition (23,24).

For example, in patients with spasticity, the reduction in the soleus muscle activity and H reflex is less pronounced during the application of a vibration to the Achilles tendon and this suggests the need to use specific vibration techniques and methodologies adapted to the specific case and pathology (25-27).

In general, to date, the literature tends to be very scarce and uncertain in relation to the effects of vibration therapy for neurological pathologies, including MS (28,29).

The aim of this study is to explore the effectiveness of new technologies, based on the application Focused Mechano-Acoustic Vibrations (FMAVs), to interact with the posture and muscle function of MS patients and to affect their quality of life and disability.

MATERIALS AND METHODS

This research is a pilot retrospective analytical observational study carried out at the "San Stef.Ar. Molise" Rehabilitation Center of Campobasso, Italy, accredited by the National Health System, in cooperation with the Ce.Fi.R.R. (Center for Physiotherapy, Rehabilitation and Re-Education) staff from March to September 2022.

The study was developed following the Good Clinical Practice (GCP) guidelines. It was conducted within the ethical principles outlined in the Declaration of Helsinki, and with the procedures defined by the ISO 9001-2015 standards for “Research and experimentation”. Written informed consent was obtained at baseline from all participants. All the procedures applied comply with the national safety regulations and the protocol is accessible to anyone who does not highlight specific contraindications (pregnancy, epilepsy, electrical implants, infections and tuberculosis) to the prescribed treatment. The protocol does not constitute an experimental practice, as applies the same procedures used at the study facility for all patients who do not present the listed contraindications. Furthermore, the Ce.Fi.R.R., as the institution in charge for carrying out the study through part of its staff, is certified for the realization of "Clinical observational studies in the rehabilitation field" (Certificate from the Italian Accreditation Body "Accredia" n. IT15/0304), in accordance with the ISO 9001:2015 standards. Due to these considerations, the lack of incontrovertible national legislation regarding the need for the submission of retrospective and/or non-pharmacological observational studies to an Ethics Committee (30) and the routine nature of the data collection performed (31), a formal Ethics Committee clearance was not required. This is intended as a pilot study, to validate or improve the study protocol.

A total of 12 patients (7 women and 5 men; Caucasian ethnicity; average age of 51 years) were enrolled within the study facility.

All patients had a diagnosis of MS and were able to maintain an upright position for at least 30 seconds. The therapeutic protocol was prescribed by a medical doctor after careful evaluation of the general health status of the patient and the possibility and convenience of intervening on his/her MS in a minimally invasive way through a complementary rehabilitation approach based on FMAVs.

To assess the musculoskeletal health status of patients before (T0) and after (T1) the therapeutic protocol, a routine evaluation of the patients was carried out using the following diagnostic tools:

- Fatigue Severity Scale (FSS): it is a 9-items scale evaluating symptoms of chronic fatigue based on the answers given by the patient to questions regarding both physical, cognitive and psychosocial fatigue (32). The total score is derived from the sum of the points assigned to answers given for each item, with each answer presenting an assigned value from 1 (no fatigue perception) to 7 (severe fatigue perception). The maximum total score is therefore 63 points, indicating a situation of extreme fatigue for the patient (32). It is considered a reliable tool to assess general fatigue in the presence of MS (32);
- Stabilometric Analysis (SA): it consists in recording the parameters of Ellipse Area (mm2), Antero-Posterior Oscillations (mm) and Lateral-Lateral Oscillations (mm) through a platform equipped with sensors on which the patient stands to register his stability (33). The device used for the observed patients was Argoplus (Fremslife S.r.l., Genova, Italy); the measuring device is composed of a large support surface, placed on the ground through four vertical load measurement sensors placed under the edges of the support surface. The instantaneous load signals are sampled at 100 Hz and combined in order to calculate the position of the COP (Center of Pressure) with a precision better than 0.1 mm in the entire supported weight range (10-200 Kg). The support surface, in honeycomb panel, has a natural resonance frequency under alternating load of over 200 Hz to ensure that all the components of the Sway are effectively transferred to the load sensors and therefore to the processing of all the harmonics of the COP oscillation in the frequency band up to 10 Hz. This assessment has proven useful in assessing the body-stabilization abilities of MS patients (33).

The observed patients underwent a protocol consisting in the application of FMAVs 3 times a week for 4 weeks, for a total of 12 sessions lasting approximately 25 minutes each. The treatments were performed on an outpatient basis in the study venue. FMAVs therapy was administered through the Vibration Sound System (ViSS) (Vissman Europe S.r.l., Rome, Italy), using vibrating plastic cups connected to the air generator of the device. The transducers were symmetrically positioned on multiple body areas of the trunk and lower limbs in which typically palpable Myofascial Trigger Points (MTrPs) might be located, in particular at the level of upper trapezius, dorsal paraspinal muscles, lumbar paraspinal muscle, rectus femoris, vastus medialis, vastus lateralis, hamstrings, gastrocnemius and tibialis anterior. During each session, the stimulation frequency was set at 120 Hz for the first 15 minutes followed by a frequency of 180 Hz applied for the remaining 10 minutes. The FMAVs treatments were administered to the patients through a device called Vibration Sound System One (Vissman S.r.l., Rome, Italy).

Given the relatively small size and demographic variability of the observed group of patients, the data collected at time T0 and T1 were processed through the application of a non-parametric Wilcoxon signed-rank test. Data analysis was performed through the Statistics Kingdom open online calculator software (https://www.statskingdom.com, Melbourne, Australia). The observed changes were considered significant for p values < 0.05.

RESULTS

At the end of the therapeutic protocol, mixed changes were observed both for FSS and SA values.

In particular, the FSS variable showed a significant reduction ($p = 0.04$) between T0 and T1, equal to an average percentage variation of -14%, going from a mean value of 49.4 ± 10.4 to 42.5 ± 11.3 (Fig.1).

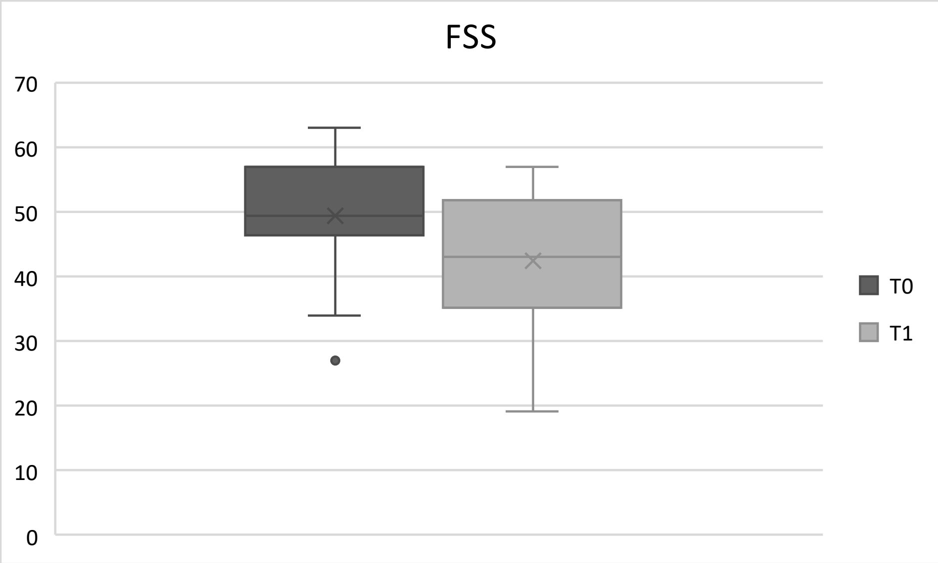

Fig. 1. *Box plots of MFIS values at times T0 and T1.*

Nevertheless, mixed results were observed in relation to the SA parameters. In fact, mainly non-significant variations of the considered values were observed, with the exception of a slight significant increase in Closed-Eyes Ellipse Area at Closed Eyes (+31.2%, p = 0.04) and Closed-Eyes Lateral-Lateral Oscillations (+16.9%, p = 0.02), as highlighted in Table I.

Table. I. *Stabilometric Analysis variations between times T0 and T1.*

	Ellipse Area (mm^2)		Antero-Posterior Oscillations (mm)		Lateral-Lateral Oscillations (mm)	
	Open-Eyes	Closed-Eyes	Open-Eyes	Closed-Eyes	Open-Eyes	Closed-Eyes
Mean	616.6	543.2	1070.1	1404.3	36.1	35.9
S.D.	644.4	373.5	948.3	1155.4	13.7	14.8
p	n.s.	0.04	n.s.	n.s.	n.s.	0.02
Δ%	-11.9	+31.2	-0.6	+11.1	+3.5	+16.9

DISCUSSION

To date, the literature regarding vibrations as a therapeutic approach in MS patients is scarce. Our study pointed out a positive correlation between FMAVs application and improvement of perceived fatigue, measured with FSS, in MS patients. However, mixed results were observed in the relationship between FMAVs application and postural stability measured with SA in the same MS patients.

It is known that vibrations, administered with different modalities and physical parameters, are able to produce a multitude of mechanical and endocrine-metabolic effects at the musculoskeletal level (34). In particular, in the context of localized FMAVs vibrations, it would seem that frequencies between 100 Hz and 200 Hz, such as those applied in our study, are endowed with myorelaxing properties compared to the hyper-tonifying proper-ties of FMAVs vibrations in the order of 300 Hz (34); this difference might be attributable to the different stimulation frequency threshold of mechanoreceptors that are found in various kind of tissue, in particular those of the skin such as Meissner and Pacinian corpuscles (34), as well as to the different changes in muscle morphology induced by different stimulation frequencies (34). However, the influence of these pathways on the perception of fatigue by subjects undergoing vibration therapy remains unclear. Typically, the application of localized vibrations or Whole-Body Vibrations (WBVs) is associated with an increase in fatigue in the human muscular system, which however tends to manifest it-self more intensely at low frequencies, in the order of 10-50 Hz (35,36), probably by virtue of a greater synchronization of the low frequencies with respect to the activation threshold of the Tonic Vibration Reflex (26).On the contrary, localized vibrations at higher frequencies, starting from approximately 100 Hz and above, would seem to be associated with an improvement in the perception of fatigue (36,37), probably by virtue of mechanisms linked to peripheral proprioception (38) and central perception of fatigue (39), mechanisms which however require further clarification. Furthermore, it is also hypothesized that localized vibrations at higher frequencies are able to improve the efficiency of joint control in stimulated subjects (40). It should be considered that other studies in the past have already highlighted how the application of localized vibrations, even of the FMAVs type, at frequencies from 120 Hz to 300 Hz would seem to be able to reduce muscle soreness (41) and perceived fatigue at a central level (42) in the human body. In light of what has been expressed so far, it is possible that the 120 Hz and 180 Hz FMAVs to which the observed MS patients were subjected actually contributed to the significant 14% reduction in the FSS score detected by the analysis of the available data.

The same factors considered in relation to the observed improvement in fatigue could have also influenced the mixed results obtained regarding the stability of patients subjected to SA. In particular, we observed how MS patients treated with the FMAVs protocol in general did not undergo particularly significant variations in postural stability in terms of oscillations and area of the ellipse in relation to the Center of Pressure. In fact, a slight increase in the reference values of SA was observed. The literature would seem to suggest that muscles respond to vibratory stimulation with plastic adaptations, which are expressed in a maximum potentiation obtained at frequencies around 300 Hz when such stimuli are applied in the form of FMAVs (43).Since the patients we observed were treated with FMAVs at frequencies between 120 Hz and 180 Hz, which are known to be associated with myorelaxant effects (23), it is possible that the stimulation frequency did not significantly influence the postural stability of MS patients. As the patients we observed were treated with FMAVs at frequencies between 120 Hz and 180 Hz, notoriously associated with myorelaxant effects (34), it is possible that the stimulation frequency did not significantly influence the postural stability of MS patients, since the applied frequencies denote a markedly more analgesic and hypotonifying activity compared to higher frequencies capable of directly strengthening the treated muscles and therefore increasing the postural stability of the treated subjects. Furthermore, since the observed patients were treated with 25 minutes of continuous application of FMAVs, it cannot be excluded that the relatively prolonged exposure time produced a rebound phenomenon of the activation of Tonic Vibration Reflex mechanisms, which apparently undergo reduction of EMG activity, motor unit firing rates, and contraction force when the involved receptors are overstimulated and irritated for a long time (44). In any case, the postural effects of the treatment seem to be amplified when the visual sensory input is removed in the patient by closing his eyes, confirming that eyes play an important role in the postural control (22) even in the case of MS patients and can in turn influence and be influenced by the peripheral muscle stimulation of a FMAVs-type treatment, raising questions about this physiological interrelationship that would merit future investigation.

Although the observed results are encouraging and interesting, some limitations of this study must necessarily be taken into account. Among the limitations of the study, it is necessary to consider the small sample size. Furthermore, the selected sample referred only to MS patients who could maintain an upright position. In fact, a choice of allocation could exaggerate the estimate of the treatment effect, on average. Furthermore, the absence of a control group and a follow up, due to the observational design, would constitute an ulterior limitation with respect to the reliability of the observed variations. Nonetheless, among the many tools that could be used in MS symptoms assessment, the scales and systems here applied are widely adopted in several studies, allowing for comparison of results across different cohorts.

About the safety of the protocol, potentially, the use of vibration cups could expose patients to an increased risk of muscle reaction (contractures and/or instability), but in our study and in our routine clinical experience this never happened, suggesting a high level of safety and minimal invasiveness of FMAVs, which was generally detected in many reviews and complex clinical contexts (45-47). A medium-term follow-up could be useful to verify the effectiveness of the vibratory treatment over time, as well as to establish how often to program any recall cycles.

One of the key strengths that must be considered is the uniqueness of the study which, to the best of our knowledge, reported for the effect of FMAVs in MS, both from the point of view of fatigue and posture.

CONCLUSIONS

In conclusion, the vibratory stimulation was well tolerated by MS patients, proved to be safe and effective, easy to use, without risk for the patient and particularly effective for reducing MS-related fatigue, which is a fundamental point to increase the autonomy of the patient and may result in a notable reduction in the support of caregivers and consequently a saving in social expenses for health.

FMAVs can influence the musculoskeletal system of the patient affected by MS, inducing changes in postural attitude and related adaptation capacities in terms of stability and relationship with visual inputs. However, the effects on the postural system determined by different vibration frequencies and times of exposure to the treatment require further study to better clarify the specific application parameters for each pathological condition.

Although there is positive evidence for the effects of FMAVs in MS patients, our experience suggests the need for further randomized studies on larger samples to determine the best frequency and the best amplitude and duration of exposure to FMAVs in order to better improve function in patients with neuromuscular alterations in MS.

Conflict of interest
The authors declare that they have no conflict of interest.

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